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CHEMOTHERAPY OF MALIGNANT LYMPHOMAS

Chemotherapeutic agents have established an important place in the therapy of malignant lymphomas (Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and giant follicle lymphosarcoma). The principal indications for chemotherapy, as an alternative to x-ray irradiation, are (1) severe systemic manifestations such as fever, anorexia, weakness and itching, in which chemotherapy may give dramatic relief; (2) widespread involvement which makes irradiation time-consuming, cumbersome or otherwise impracticable; (3) conditions such as spinal-cord or ureteral compression or the vena caval syndrome, in which rapid tumor shrinkage is required, and in which the initial inflammatory edematous reaction sometimes induced by x-ray cannot be risked; (4) such symptoms as fatigue, anemia, mild fever, and night sweats without significant adenopathy in a patient known to have a lymphoma (search should, of course, be made for other possible causes of the symptoms before an anti-cancer drug is used); (5) a history of previous intense irradiation of lesions which may contraindicate additional x-ray treatment.

The remissions induced by courses of chemotherapy are of variable effect and duration. For prolonged shrinking of individual tumor masses, x-ray irradiation is likely to be much more effective than chemotherapy, usually with less inconvenience and hazard to the patient. The drugs commonly used for malignant lymphomas include nitrogen mustard (Mustargen Hydrochloride - Merck); Triethylene Melamine (TEM - Lederle); triethylene thiophosphoramide (Thio-TEPA - Lederle); chlorambucil (Leukeran - Burroughs, Wellcome), cyclophosphamide (Cytoxan - Mead, Johnson), and the corticosteroid hormones.

MUSTARGEN - Nitrogen mustard, the first agent introduced, is the drug of choice, especially for patients requiring an immediate response. This is the opinion of all of the cancer investigators and clinicians in major cancer research centers who were consulted in the preparation of this appraisal. The preferred adult dosage is 0.4 mg./kg., which may be given as a single injection, or divided into two doses given on successive days. To avoid the hazard of extravasation, the injection is best given through a fine needle into the tubing of a rapidly running saline infusion. Nausea and vomiting often occur one to eight hours after an injection. The most important toxic effect of nitrogen-mustard therapy is bone-marrow depression. This is not ordinarily a serious problem if the usual tests for bone-marrow depression are carried out.

LEUKERAN - Leukeran is less effective than nitrogen mustard, but it is the oral agent of choice. In the usual daily dosage range of 0.1 to 0.2 mg./kg. it produces relatively few side effects. Therapy is continued for 21 to 30 days or longer, depending on therapeutic response and on the results of frequent blood examinations. The total dosage for a course of treatment in the average adult ranges from 200 to 600 mg. Maintenance therapy has been attempted, but its value has not been established. Therapeutic effects may be seen as early as several days after the start of therapy, and are maximal at 3 to 5 weeks. It is best to give intermittent courses, with a new course starting after recovery from a depressed blood picture or with recurrent activity of the disease. The dosage schedule should be adjusted to each patient. Excessive doses or prolonged treatment at high dosage levels can induce severe bone-marrow depression.

THIO-TEPA - The usual dose of Thio-TEPA, equivalent to a course of nitrogen mustard, is 0.2 mg./kg. given parenterally on four successive days. Therapeutic response appears to be less satisfactory than with nitrogen mustard. Along with a number of other polyfunctional alkylating agents, Thio-TEPA does not appear to have any advantage over the drugs discussed above.

TEM - Triethylene Melamine is effective in relieving systemic symptoms. Like Leukeran, TEM has the advantage of oral therapy and it induces relatively little nausea and vomiting. Since the acid environment of the stomach tends to inactivate it, with consequent erratic absorption and variation in both effectiveness and toxicity, each dose should be administered after an overnight fast; it should be given along with one to two grams of sodium bicarbonate and two glasses of water to speed its passage through the stomach. Even with these precautions, however, the effects of a particular dose are less predictable than with nitrogen mustard or Leukeran. The dosage of TEM is usually 2.5 or 5 mg., given for one day or repeated for two or three successive days. Further treatment, at weekly intervals, depends on the blood picture and on clinical response. Over a one-month period the usual total dose is 20 to 40 mg. Many therapists have stopped using TEM because manifestations of bone-marrow toxicity may be delayed, may persist for long periods or prove irreversible.

CYTOXAN - Cytoxan, a cyclic phosphamide ester of nitrogen mustard, is similar in its effects to other alkylating agents (Medical Letter, 2:21, March 18, 1960). There is not yet enough experience with this drug to warrant its use in place of nitrogen mustard except by investigators. At this point, its main disadvantages are the frequency with which it causes alopecia and its high cost.

STEROIDS - Adrenal steroids may suppress symptomatic manifestations of malignant lymphomas, induce some degree of euphoria, and control such complications as hemolytic anemia and the bleeding of thrombocytopenia. Symptoms such as fever usually recur fairly soon, despite continued therapy. It is often claimed that corticosteroids "stimulate" the bone marrow, or "protect" the bone marrow from nitrogen-mustard or x-ray toxicity; critical studies do not substantiate these claims. Furthermore, steroids appear to be used too frequently or started too early in the treatment of malignant lymphomas, when other therapy should be used instead. Steroid therapy is most useful in the occasional cases where it is able to provide relatively long-term control of hemolytic anemia.

EFFECT OF MEALS ON ABSORPTION OF ORAL ANTI-INFECTIVE AGENTS

The effectiveness of an oral anti-infective agent may depend partly on when it is taken - whether on an empty stomach or after a meal. For example, recent studies with erythromycin propionate (H. A. Hirsch and M. Finland, Am. J. Med. Sci., 237:693, 1959 and H. A. Hirsch, et al., Am. J. Med. Sci., 239:194, 1960) show that the form in which this antibiotic is taken determines whether or not it is affected by food; the capsules should be taken on an empty stomach for maximum absorption whereas the lauryl sulfate suspension is not affected by food and can be taken at any time.

Because of chelating and other effects, food impairs the absorption of all the tetracyclines, and probably also of penicillin. The fact that penicillin is destroyed to a variable degree by acids is, however, the main reason for giving penicillin G tablets (including those containing buffering salts) on an empty stomach. Although penicillin V and Syncillin are not significantly affected by gastric acidity, it is probably best to administer all oral penicillins on an empty stomach. Novobiocin, on the other hand, appears to be more stable in an acid medium, and is therefore probably best given immediately after meals.

Some agents (see table) may be irritating when taken in the fasting state (causing nausea and vomiting) and may have to be taken after meals despite the impaired absorption. Some agents may be administered orally solely for their local effect in the intestines; these include streptomycin, neomycin, kanamycin, nystatin, nitrofurantoin, and insoluble sulfa drugs. Since systemic absorption of these agents by this route is slight, it makes no difference whether they are administered before or after meals. As a general rule, optimal absorption from the gastrointestinal tract is achieved when oral anti-infective agents are taken on an empty stomach, that is, about one hour before or at least three hours after meals. The following table summarizes available information on the time of oral administration of the various agents for maximum effectiveness.

	Before meals	After meals	Indifferent
Penicillins (G, V and Syncillin)	x		
Tetracyclines (including Declomycin)*	x		
Erythromycins* (see lauryl sulfate below)	x		
Triacetyloleandomycin (Tao; Cyclamycin)*	x		
Griseofulvin (Grifulvin; Fulvicin)*	x		
Nitrofurantoin (Furadantin)* and furaltadone (Altafur)*	x		
Novobiocin		x	
Erythromycin propionate (Ilosone) lauryl sulfate*			x
Streptomycin			x
Neomycin			x
Kanamycin (Kantrex)			x
Nystatin (Mycostatin)			x
Chloramphenicol (Chloromycetin)			x
Sulfonamides (soluble and insoluble)			x

*May have to be taken after meals to minimize irritation.

PREMARIN FOR BLEEDING

Premarin (Ayerst), a conjugated equine estrogen, is promoted as "the physiologic hemostat" to "control spontaneous hemorrhage" such as "epistaxis, ocular hemorrhage, bronchial hemorrhage, gingival bleeding, bleeding from esophageal varices, hemorrhage in peptic ulcer, gastrointestinal bleeding, rectal bleeding, hematuria due to renal and prostatic bleeding," and "to minimize blood loss during surgery, to maintain a clearer operative field, to lessen incidence of post-op hemorrhage...in surgery of every type."

In normal dogs, intravenous Premarin increases prothrombin and "accelerator globulin" and causes a slight fall in antithrombin (J. F. Johnson, Proc. Soc. Exp. Biol. & Med., 94: 92, 1957). Even if this agent should have the same effects in man, there is no reason to believe that any of these factors are abnormal in most instances of spontaneous bleeding or surgical bleeding, or that elevation of prothrombin or accelerator globulin above normal serves any useful purpose.

CLINICAL STUDIES - The published clinical studies favorable to the drug are strong on enthusiasm and weak on controls. One study, with alternate patients receiving Premarin, indicated that it was very effective in reducing bleeding after tonsillectomy (S. L. Fox, Eye, Ear, Nose and Throat Monthly, 39: 251, 1960), but no attempt was made at "blind" evaluations. A recent well-controlled study on the use of Premarin in prostatic surgery (W. H. Cooner and H. M. Burros, J. Urology, 83: 64, 1960) failed to show that Premarin was of any value in controlling blood loss during or after surgery. Investigators consulted by The Medical Letter state that they failed to demonstrate any effect of Premarin on the coagulation mechanism or capillary fragility in a variety of surgical procedures. Present evidence does not justify its use as a "hemostat" in surgery or to control spontaneous hemorrhage. The use of Premarin and other estrogen preparations in menopause will be discussed in a future report.

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